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Stereoselective synthesis of α-hydroxycyclopropanecarboxylic acids

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Abstract

Cyclopropanation of chiral α-alkoxy acrylamides derived from 1*R*,2*S*-ephedrine and α-keto acids provides cyclopropyl morpholinones with good diastereoselectivity. Removal of the ephedrine portion generates α-hydroxycyclopropane carboxamides which are readily converted to enantiomerically enriched α-hydroxycyclopropanecarboxylic acids.

Keywords: Stereocontrol; acrylamides; cyclopropanes; hydroxy acids

The asymmetric synthesis of α-hydroxy acids continues to be actively investigated due to their utility as chiral building blocks for the synthesis of natural products and biologically active molecules[1,2]. α-Hydroxycyclopropanecarboxylic acids constitute a unique class of hydroxy acids due not only to their structural novelty but also their applications in the synthesis of five and six membered ring systems[3], as enzyme inhibitors[4], and components of fungicides and agricultural microbicides[5,6]. Herein, we describe preliminary results on a new approach to these molecules that involves asymmetric cyclopropanation of chiral α-alkoxy acrylamides.

The only reported method for the asymmetric synthesis of α-hydroxycyclopropane carboxylic acids, involves a stereoselective ring contraction of enantiomerically enriched 3-methyl cyclobutane-1,2-diones which are prepared from the corresponding succinates[3]. A potential alternative, which has been demonstrated on racemic, diastereomerically pure 2-ethyl 1-aminocyclopropane-1-carboxylic acids, involves diazotization in acetic acid to yield the corresponding acetoxy acids with retention of stereochemistry[7]. To the best of our knowledge, the synthesis of hydroxycyclopropanecarboxylic acids by cyclopropanation (asymmetric or otherwise) of substituted α-alkoxy (or acyloxy) acrylamides or acrylates has not been reported. We chose to investigate this approach by employing ephedrine-derived acrylamides as substrates for asymmetric cyclopropanation.

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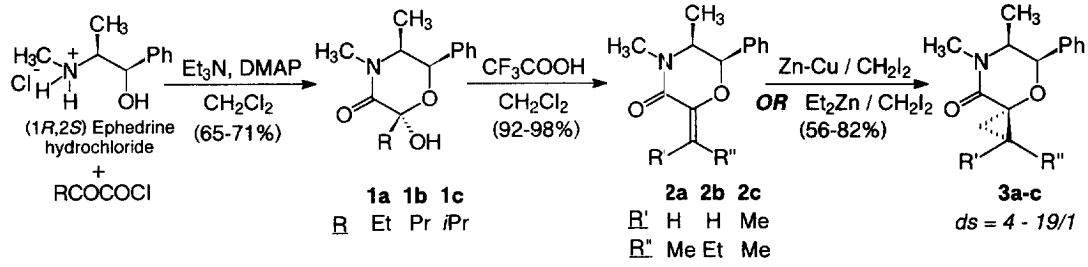
Acylation of 1*R*,2*S*-ephedrine hydrochloride with aliphatic α-keto acid chlorides generates the hemiacetals **1**, which are readily dehydrated to the the chiral acrylamides **2**[8] in good yield (Scheme 1). These served as starting materials for this study. The olefins **2a** and **2b** have been assigned the *Z* geometry on the basis of the chemical shift of the olefinic methine proton (δ 6.12 in **2a**) as compared to the upfield shift[8] in the *E* isomer (δ 5.75) which was obtained by irradiation of **2a** at 254 nm.



Scheme 1

Initial studies were conducted on acrylamide **2a**. Somewhat unexpectedly, **2a** was unreactive towards CH_2N_2[9] which suggests that the acrylamide in **2** may be deactivated for 1,3-dipolar cycloadditions by the α-alkoxy substituent. The addition of a catalytic amount of $Pd(OAc)_2$[10] had no effect on the reaction. However, conventional Simmons-Smith cyclopropanation[11] of **2a** employing Zn-Cu/CH_2I_2 in ether was successful and afforded the cyclopropyl morpholinone **3a** in 62% yield (Scheme 1). The reaction proceeded only at the solvent reflux temperature and stereoselectivity was moderate. Thus, in diethyl ether, **3a** is obtained as a 3/1 mixture of diastereomers whereas the use of DME or THF marginally increases the selectivity to 4/1. Lower reaction temperatures are beneficial and cyclopropanation with the Et_2Zn/CH_2I_2 derived reagent[12] at ambient temperature generates **3a** with 16/1 diastereoselectivity (Table 1). The diastereomer ratio was readily determined by ^1H NMR spectroscopy of the crude product and is based on the integration of the characteristic benzylic methine resonance (doublet in the 5 ppm region) due to the ephedrine portion. Cyclopropanation of **2** could not be effected with the reagent derived from Me_3Al/CH_2I_2[13]. The procedure for cyclopropanation of **2c** with Et_2Zn/CH_2I_2 is representative.[1]

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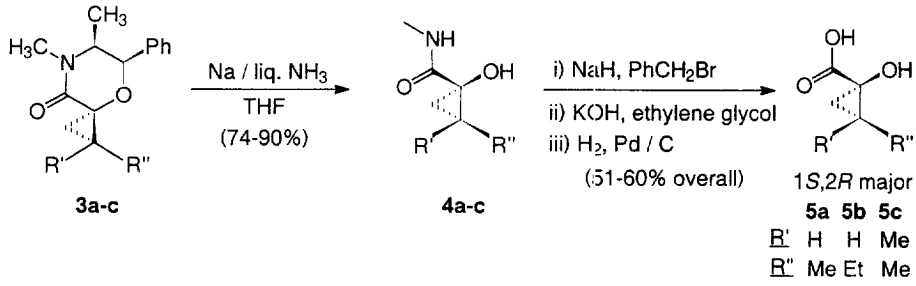
[1]**Cyclopropanation of 2c with Et_2Zn/CH_2I_2:** To a solution of **2c** (0.047 g, 0.19 mmol) in anhydrous ether (1 mL) at -78 °C was added diethylzinc (1M solution in ether[14], 2 ml, 2 mmol) followed by diiodomethane (0.16 mL, 2 mmol). After 5 min. the reaction mixture was warmed to ambient temperature and stirred for 12 h after which it was cooled to -78 °C, additional Et_2Zn and CH_2I_2 were added (2 mmol each) and the reaction was continued for 12 h at ambient temperature. The mixture was diluted with ether and the solution was washed with HCl (2N, 2x5 ml) follwed by water (4x5 ml). The ether solution was dried (Na_2SO_4) and concentrated to give 64 mg of crude **3c** (ds =19/1 by ^1H NMR). Purification by flash chromatography on silica gel furnished 34 mg (69%, 82% based on recovered **2c**) of **3c**. IR ($CHCl_3$): 2979, 2927, 1652, 1448, 1398, 1377, 1339, 1295, 1254, 1207, 1180, 1097, 1070, 1026, 968, 885 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (Major isomer) δ 7.50-7.20 (m, 5H, Ar*H*), 5.10 (d, 1H, *J* = 2.7, C*H*Ph), 3.55 (dq, 1H, *J* = 2.7, 6.5, C*H*CH_3), 3.05 (s, 3H, NCH_3), 1.45 (s, 3H, CCH_3), 1.40 (s, 3H, CCH_3), 1.35 (d, 1H, *J* = 4.5, CH_2), 1.00 (d, 3H, *J* = 6.5, CHCH_3), 0.80 (d, 1H, *J* = 4.5, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) (Major isomer) δ 168.6 (*C*=O), 138.1 (Ar*C*), 128.0 (Ar*C*H), 127.2 (Ar*C*H), 125.2 (Ar*C*H), 76.0 (Ph*C*H), 66.1 (*C*-O), 59.2 (CH_3CH), 33.5 (NCH_3), 28.8 (*C*H_2), 27.0 (*C*$(CH_3)_2$), 21.4 ($CHCH_3$), 19.9 (CCH_3), 12.3 (CCH_3); MS (70 eV) m/z 78 (2), 83 (11), 91 (8), 105 (3), 117 (100), 131 (1), 142 (63), 148 (3), 189 (1), 204 (1), 259 (M^+, 1); Analysis for $C_{16}H_{21}NO_2$: Calcd: C 74.09, H 8.16, N 5.40; Found: C 73.96, H 8.29, N 5.41; $[\alpha]^{25}_D$ = -167.4 (c 1, $CHCl_3$).

The absolute configuration of the major diastereomer in **3a** was determined by conversion of **3a** (obtained from the Zn-Cu/CH_2I_2 cyclopropanation of **2a**) to the known α-hydroxy cyclopropane carboxylic acid **5a**[3]. Dissolving metal reduction of **3a** (Na/liq. NH_3 in THF) generates the hydroxy amide **4a** (74%). Hydrolysis of the amide was achieved by protection of the free hydroxyl group as a benzyl ether (NaH, $PhCH_2Br$, 63%) followed by treatment with KOH in ethylene glycol (120 °C, 87%).[2] Debenzylation by hydrogenolysis (1 atm. H_2, Pd/C, 93%) afforded **5a** with the 1*S*,2*R* configuration ($[\alpha]_D$ -32.4 (c 1.6, $CHCl_3$); Lit.[3]$[\alpha]_D$ -57 (c 1.6, $CHCl_3$) for 1*S*,2*R* **5a**; Scheme 2) in an overall yield of 51% from **4a**.[2] The above reaction sequence constitutes a new, stereoselective route to α-hydroxycyclopropanecarboxylic acids.



Scheme 2

Acrylamides **2b** and **2c** were also readily cyclopropanated with good stereoselectivity employing the Et_2Zn/CH_2I_2 derived reagent to give morpholinones **3b** (19/1) and **3c** (19/1) respectively. Although the diastereoselectivity for **3b** (4/1) obtained with the Zn-Cu/CH_2I_2 reagent is the same as that for **3a**, **3c** is obtained with good diastereoselectivity (15/1) even at the DME reflux temperature (Table 1). The large increase in selectivity may be attributed to the increased steric demands of the substrate (tetrasubstituted double bond in **2c**). The cyclopropyl morpholinones **3b,c** were converted to the free hydroxy acids **5b** and **5c** *via* the hydroxy amides **4b,c** as described for **3a**. The configuration of **5b** (1*S*,2*R*) and **5c** (1*S*) is

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[2] **(*1S,2R*)-2-Methyl-1-hydroxycyclopropane-1-carboxylic acid (5a)**[3]: A mixture of the *N*-methyl *O*-benzyl amide obtained from **4a** (0.05 g, 0.23 mmol) in ethylene glycol (2 mL) and KOH (0.128 g, 2.28 mmol) was heated at an oil bath temperature of 120°C for 48 h. The reaction mixture was acidified with conc. HCl and extracted with CH_2Cl_2. The CH_2Cl_2 solution was extracted with saturated aq. $NaHCO_3$. The $NaHCO_3$ layer was acidified with conc. HCl and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated to furnish 0.041 g (87%) of *O*-benzyl **5a** that was pure by ^1H NMR. IR (neat): 3750, 3648, 3032, 2932, 2360, 1694, 1497, 1455, 1302, 1256, 1181, 1106, 1082, 1047, 1028, 995, 904, 836 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.25 (br s, 1H, COO*H*), 7.55-7.30 (m, 5H, Ar*H*), 4.90 (d, 1H, *J* = 10.9, CH_2Ph), 4.65 (d, 1H, *J* = 10.9, CH_2Ph), 1.95-1.75 (m, 1H, $CHCH_3$), 1.60 (dd, 1H, *J* = 4.8, 9.6, CH_2), 1.35 (d, 3H, *J* = 6.0, CH_3CH), 0.95 (dd, 1H *J* = 4.8, 7.5, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.0 (C=O), 137.9 (ArC), 128.3 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 72.3 (CH_2Ph), 63.0 (*C*-O), 24.7 (CH), 22.7 (CH_2), 12.5 (CH_3CH); MS (70 eV) m/z 91(100), 118(25), 161(2); $[\alpha]^{25}_D$ = -30.1 (c 3.3, $CHCl_3$).

A solution *O*-benzyl **5a** (0.15 g, 0.73 mmol) in ethanol (20 mL) was hydrogenated over 10% Pd/C (0.03 g) at ambient temperature and atmospheric pressure for 6 h. The catalyst was removed by filtration through celite and the filtrate was concentrated to furnish 0.079 g (93%) of **5a** which was pure by ^1H NMR. IR ($CHCl_3$): 3404(br), 1710(br), 1165 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.85 (br s, 2H, O*H*, COO*H*), 1.75-1.50 (m, 2H, CH_2, C*H*), 1.25 (d, 3H, CH_3), 0.95-0.80 (m, 1H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.7 (*C*=O), 57.0 (*C*-O), 23.6 (CH_2), 23.1 (CH), 11.8 (CH_3); $[\alpha]^{25}_D$ = -32.4 (c 1.6, $CHCl_3$).

assigned by analogy to **5a**. The enantiomeric excess of the α-hydroxy acids (obtained form the $Zn\text{-}Cu/CH_2I_2$ reagent) is based on the diastereomeric excess of the precursors **3** since epimerization of the newly generated stereocenters during conversion of **3** to **4** and **4** to **5** is unlikely. The results are summarized in Table 1.

The facial selectivity for cyclopropanation of **2** may be explained by considering a transition state conformation for **2** in which the phenyl group is *quasi* equatorial[8]. An axial approach of the cyclopropanating species would result in the observed stereoselectivity.

Table 1

Stereoselective cyclopropanation of **2** to **4** and conversion of **4** to **5**

Substrate	Reagent	% yield 3	ds 3[a]	% yield 4	% yield 5[b]	er[c] 5[d]
2a	$Zn\text{-}Cu/CH_2I_2$	62	4/1	74	51	4/1
	Et_2Zn/CH_2I_2	56[e]	16/1			
2b	$Zn\text{-}Cu/CH_2I_2$	58	4/1	85	60	4/1
	Et_2Zn/CH_2I_2	59	19/1			
2c	$Zn\text{-}Cu/CH_2I_2$	69	15/1	90	58	15/1
	Et_2Zn/CH_2I_2	82[e]	19/1			

a: determined by ^1H NMR spectroscopy b: overall yield for three steps c: based on the ds for 3 d: prepared from 3 obtained by the $Zn\text{-}Cu/CH_2I_2$ cyclopropanation e: based on recovered **2**.

In conclusion, an asymmetric synthesis of α-hydroxycyclopropanecarboxylic acids has been achieved by cyclopropanation of chiral α-alkoxy acrylamides. It is noteworthy that enantiomerically enriched hydroxy acids such as **5c**, which are symmetrically disubstituted on C2, may not be readily available by ring contraction[3] of the corresponding cyclobutane-1,2-dione since it is achiral. The present method thus offers a distinct advantage. Current efforts focus on other reactions of **2**.

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